REMARKS

Introduction:

Claims 26-40 are pending in the present application. Applicants are canceling herewith Claims 26-29. Applicants are adding herewith new Claim 40. Following the present amendments, Claims 30-41 will be pending and subject to examination.

The Office Action:

Claims 29-40 were rejected under 35 U.S.C. § 112, first paragraph, as being not enabling for inhibition of neovascularization. Claims 29-40 were rejected under 35 U.S.C. § 112, second paragraph, as failing to comply with the written description requirement. Claims 29, 30, 32, 33, 35, 36, 38 and 39 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 46-62 of copending application Serial No. 10/280,831. Claims 29-40 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 46-62 of copending application Serial No. 10/080,076. Claims 29-40 were rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 1, 2, 5 and 7 of U.S. Patent No. 5,504,074. Claims 29-40 were rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 1, 4, 6 and 8 of U.S. Patent No. 5,661,143. Claims 29, 30, 35, and 36 were rejected under 35 U.S.C. § 102(b) as being completely anticipated and unpatentable over the article by Seegers et al. Claims 31-34 and 37-40 were rejected under 35 U.S.C. § 103(a) as being obvious and unpatentable over the article by Seegers et al. Applicants respectfully traverse the foregoing rejections.

The Rejections Under 35 U.S.C. § 112:

Claims 29-40 were rejected under 35 U.S.C. § 112, first paragraph, as being not reasonably providing enablement for inhibition of neovascularization not due to angiogenesis. The rejection states that the claimed compounds have anti-mitotic activity that was "evaluated by testing their ability to inhibit the proliferation of new blood vessel cells (angiogenesis)." The rejection then defines angiogenesis as the process of neovascularization from pre-existing blood vessels. The rejection states that the term neovascularization is broader that angiogenesis and includes proliferation of blood vessels in tissue not normally containing them or proliferation of blood vessels of a different kind than usual in a tissue. The rejection concludes that the present specification lacks examples of proliferation of blood vessels in tissue not normally containing them or of a different kind than usual in a tissue, and, thus, does not provide guidance to enable the skilled artisan to practice the claimed invention commensurate in scope with the instant claims. Applicants respectfully disagree.

All neovascularization in a human or animal is associated with angiogenesis.[1] Therefore, the term neovascularization is not broader than angiogenesis, as stated by the examiner as the basis for the rejection. Attached hereto is the definition of the term "neovascularization" provided in the Merriam Webster Medical Dictionary. Neovascularization is defined as:

> Vascularization especially in abnormal quantity (as in some conditions of the retina) or in abnormal tissue (as a tumor).

The specification of the present invention states that the CAM assay and the assay disclosed in the examples are useful in identifying compounds useful in treating diseases such as,

[1] The formation of blood vessels where none previously existed is termed vasculogenesis and only occurs during embryogenesis.

ocular angiogenic diseases including diabetic retinopathy and macular degeneration. Specification at pages 6-7. In these diseases, the new blood vessels are formed from sprouts formed on existing blood vessels in surrounding tissue. The sprouts then grow to invade the tissue needing the blood supply. The specification also discloses that the compounds are useful in treating solid tumors. The formation of new blood vessels associated with diabetic retinopathy and macular degeneration and the formation of new blood vessels associated with solid tumors are precisely the examples of new blood vessel formation provided in the Merriam Webster Medical Dictionary definition of "neovascularization."

Thus, the distinction drawn by the examiner between angiogenesis and neovascularization is incorrect. As stated above, the term "neovascularization" is not broader than the term angiogenesis, as suggested by the examiner. Thus, the term "neovascularization" is properly used in the present claims, and the specification provides sufficient disclosure to test and identify compounds useful for treating neovascularization. Therefore, it is submitted that the present specification is enabling for the present claims and that the claims comply with 35 U.S.C. § 112, first paragraph. Accordingly, it is respectfully requested that the rejection of Claims 29-40 as lacking enablement should be withdrawn.

Claims 29-40 were also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. As an example, the rejection states that R_1 having "up to 10 carbons or heterocycle" lacks written description. Applicants are canceling herewith Claim 29. Therefore, applicants submit that this rejection is now moot. Accordingly, applicants request that the rejection of Claims 29-40 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement should be withdrawn.

The Provisional Rejections:

Claims 29, 30, 32, 33, 35, 36, 38 and 39 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 46-62 of copending application Serial No. 10/280,831. Claims 29-40 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 46-62 of copending application Serial No. 10/080,076. Since these are provisional rejections, it is submitted that no response is required at this time and the provisional rejections cannot form a basis for denying allowance of the present claims.

The Double Patenting Rejections:

Claims 29-40 were rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 1, 2, 5 and 7 of U.S. Patent No. 5,504,074. Claims 29-40 were rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 1, 4, 6 and 8 of U.S. Patent No. 5,661,143. Accordingly, applicants are submitting herewith a terminal disclaimer with respect to U.S. Patent Nos. 5,504,074 and 5,661,143 in compliance with 37 CFR 1.321. Applicants are also submitting herewith the fee required by 37 CFR 1.20(d). Applicants submit that the filing of the terminal disclaimer overcomes the present rejection. Accordingly, applicants respectfully request that the rejection of Claims 29-40 on the basis of obviousness-type double patenting in view of U.S. Patent Nos. 5,504,074 and 5,661,143 be withdrawn.

The Rejection Under 35 U.S.C. § 102:

Claims 29, 30, 35, and 36 were rejected under 35 U.S.C. § 102(b) as being

completely anticipated and unpatentable over the article by Seegers et al. The rejection states that Seegers et al. teach the antimitotic properties of 2-methoxyestradiol. Applicants respectfully disagree.

Seegers et al. discloses that 2-methoxyestradiol is anti-mitotic and suggests that it "may be the ultimate cytotoxic compound". Seegers et al. merely describe 2-methoxyestradiol as **cytotoxic**. Such a compound would be considered by one skilled in the art as nothing more than an **indiscriminant poison**. Any substance defined as "toxic" will kill a cell, but the mere toxicity of a substance does not make it useful for the treatment of diseases in humans and animals, such as neovascularization. A useful therapeutic agent is one that is **selectively** toxic to abnormal cells, but minimally toxic to normal cells. Few anti-mitotic compounds are selectively toxic. Although it is generally accepted by those skilled in the art that microtubule inhibitors are likely to be selective for cancer cells, many anti-mitotic compounds that interfere with spindle formation fail to interfere with microtubules. That is because spindle formation involves components other than microtubules. As described in the attached scientific paper of Maro *et al.*, "Mechanism of polar body formation in the mouse oocyte: an interaction between the chromosomes, the cytoskeleton and the plasma membrane", *J. Embryol. exp. Morph.* 92:11-32 (1986), spindle figure formation depends upon the ability of clusters of chromosomes to become redistributed in the cell by an actin filament-dependent process, organize into spindles, and rotate to yield polar bodies. In this process of spindle formation, the chromosome clusters both promote tubulin polymerization in their vicinity and recruit microtubule-organizing centers, which organize the polymerized tubulin into spindles. In addition, each chromosome cluster induces a focal accumulation of subcortical actin. The chromosomes are anchored to the microtubules by kinetochores linked to motor proteins. Thus, the following three major

components are necessary for proper spindle figure and polar body formation: 1) microtubules; 2) actin filaments; and 3) kinetochores with motor proteins. Interference with the formation or binding of any of these three components results in abnormal spindle figure formation.

Only **after** realizing that 2-methoxyestradiol had anti-microtubule activity *in vitro* and could inhibit cell proliferation *in vivo* did applicants conclude that 2-methoxyestradiol could be useful for the treatment of neovascularization. Applicants discovered the anti-microtubule activity of 2-methoxyestradiol by observing an inhibition of microtubule assembly in an *in vitro* turbidity assay (as described on page 6, lines 4-22 of the specification) and observed the inhibition of cell proliferation of new blood vessel cells *in vivo* in chick embryos, a model which mimics the growth of blood vessels in tumors. (Cancers are generally made up of tumor cells infiltrated with blood vessels, both of which are abnormally, rapidly proliferating. The chick embryo chorioallantoic membrane (CAM) assay is described on page 5, line 17-page 6, line 2 of the specification.)

In view of the fact that the Seegers et al. paper **fails** to disclose to one of ordinary skill in the art that 2-methoxyestradiol is a microtubule inhibitor, one would be **unable** to conclude that 2-methoxyestradiol could be used to treat the presently claimed diseases. And, in fact, the Seegers et al. paper **fails** to disclose a single disease that is treatable with 2-methoxyestradiol.

In order for the Seegers et al. paper to anticipate the presently claimed invention, Seegers et al. must disclose each and every element of the claimed invention. Since the Seegers et al. paper does not disclose the use of 2-methoxyestradiol to treat any diseases in humans or animals, applicants submit that the rejection of Claims 29, 30, 35, and 36 under 35 U.S.C. §

102(b) as being completely anticipated and unpatentable in view of the publication by Seegers et al. is improper and should be withdrawn.

The Rejection Under 35 U.S.C. § 103:

Claims 31-34 and 37-40 were rejected under 35 U.S.C. § 103(a) as being obvious and unpatentable over the article by Seegers et al. The rejection states that Seegers et al. teach the antimitotic properties of 2-methoxyestradiol. The rejection further states that the instant claims differ from the reference by reciting inhibition of ocular neovascularization. The rejection concludes that the ordinary artisan would have reasonably expected that 2-methoxyestradiol would inhibit cell mitosis in any tissue, including ocular tissue. Applicants respectfully disagree.

Rather than restating the same arguments as set forth above regarding the rejection under 35 U.S.C. § 102, applicants incorporate herein by reference those same arguments. As stated above, Seegers et al. merely describe 2-methoxyestradiol as **cytotoxic**. Such a compound would be considered by one skilled in the art as nothing more than an **indiscriminant poison**. Therefore, one cannot extrapolate, as the rejection suggests, from the *in vitro* studies of Seegers et al. to the *in vivo* treatment of diseases in humans and animals, because it would not be obvious to administer an indiscriminate poison to a human or animal. Seegers et al. does not disclose whether 2-methoxyestradiol can be selectively cytotoxic, and no suggestion of such is provided, either. In view of the foregoing, one of ordinary skill in the art could not conclude from Seegers et al. that 2-methoxyestradiol could be used to treat the claimed diseases in humans and animals. Accordingly, applicants submit that the rejection of Claims 31-34 and 37-40 under 35 U.S.C. § 103(a) as being obvious and unpatentable in view of the publication by Seegers et al. is improper and should be withdrawn.

The New Claim:

Applicants are canceling herewith independent Claim 29 and are adding in its place new Claim 42. Support for this new claim can be found generally throughout the specification. Additionally, support for this claim can be found in original Claim 1. On page 17 of the specification, it is stated that when each R_b, R_c, R_d, R_e, R_i, R_j, R_k, R_L, R_m and R_o is H; R_f is $-CH_3$; Rg is -OH; Z' is >COH; and Z" is $>CH_2$; then R_a is not –H. This condition produces the subgenus defined by Claim 42. Thus, applicant submits that there is support under 35 U.S.C. §112 and the addition of Claim 42 does not add any new matter.

Conclusion:

Applicants respectfully request reconsideration of the present application in view of the foregoing remarks. Such action is courteously solicited. Applicants submit that all claims are now in condition for allowance. Applicants further request that the Examiner call the undersigned counsel if allowance of the claims can be facilitated by examiner's amendment, telephone interview or otherwise.

Respectfully submitted,

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